AGENDA
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
September 14 - 17, 2010

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2010-0481

U.S. Environmental Protection Agency
Conference Center - Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

Reevaluation of the Human Health Effects of Atrazine: Review of Non-cancer Effects and Drinking Water Monitoring Frequency

Please note that all times are approximate (see note at end of Agenda).

Day 1
Tuesday, September 14, 2010

8:30 a.m. **Opening of Meeting and Administrative Procedures** – **Joseph Bailey**, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Introduction and Identification of Panel Members** – **Steven G. Heeringa, Ph.D.**, FIFRA Scientific Advisory Panel Session Chair

8:40 a.m. **Welcome and Opening Remarks** – **Steven Bradbury, Ph.D.**, Acting Director, Office of Pesticide Programs, EPA

8:50 a.m. **Welcome and Introductions** – **Tina Levine, Ph.D.**, Director, Health Effects Division, Office of Pesticide Programs, EPA

9:00 a.m. **Atrazine Re-evaluation: Introduction and Status** – **Anna Lowit, Ph.D.**, Health Effects Division, Office of Pesticide Programs, EPA

9:30 a.m. **Evaluation of Atrazine Non-Cancer Epidemiology Literature - Carol Christensen, Ph.D., M.P.H.**, Health Effects Division, Office of Pesticide Programs, EPA

10:30 a.m. **Break**

10:45 a.m. **Atrazine: Proposed Updates to the Dose-Response Assessment - Chester Rodriguez, Ph.D.**, Health Effects Division, Office of Pesticide Programs, EPA

12:00 p.m. **Lunch**

1:15 p.m. **Approaches to Evaluating Water Sampling Strategies and Frequency of Monitoring** - **Nelson Thurman, M.S.** and **Mary Frankenberry**, Environmental Fate and Effects Division, Office of Pesticide Programs, EPA

2:15 p.m. **Scientific Considerations in Potential Sensitivity of Infants and Children and Implications of MOA on Water Monitoring Strategy** - **Anna Lowit, Ph.D.**, Health Effects Division, Office of Pesticide Programs, EPA

3:15 p.m. **Break**

3:30 p.m. **Atrazine Re-evaluation: Summary and Next Steps** - **Anna Lowit, Ph.D.**, Health Effects Division, Office of Pesticide Programs, EPA

5:00 p.m. **Adjourn**

Day 2
Wednesday, September 15, 2010

8:30 a.m. **Opening of Meeting and Administrative Procedures** – **Joseph Bailey**, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Introduction and Identification of Panel Members** – **Steven G. Heeringa, Ph.D.**, FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. **Follow-up from Previous Day's Presentations**

9:15 a.m. **NIEHS Presentation** - **Suzanne Fenton, Ph.D.**, Cellular and Molecular Pathology Branch, National Institute of Environmental Health Sciences

10:00 a.m. **Break**

10:15 a.m. **Public Comment**

12:30 p.m. **Lunch**

1:30 p.m. **Public Comment**

3:30 p.m. **Break**

3:45 p.m. **Charge To Panel - Question 1.0 - Non-cancer Epidemiology**

Section 3.0 and Appendix B of the draft Issue Paper provide the Agency reviews and synthesis of the non-cancer epidemiology studies available for atrazine. These include studies on a variety of topics, notably female and male reproductive outcomes and birth outcomes in addition to other topics. Section 4.0 integrates the findings of the epidemiology and experimental toxicology studies.

Question 1.1

Please comment on the sufficiency of the Agency's non-cancer epidemiology reviews with respect to identifying the major strengths and limitations of each study.

4:30 p.m. **Charge To Panel**

Question 1.2

At this time, atrazine's non-cancer epidemiologic database is not robust enough for inclusion in quantitative risk assessment and does not support the ability to determine causal associations. There are several limitations present in the current database, and the quality of atrazine exposure assessment is paramount among the limitations. In Section 4.0 of the draft Issue Paper, the Agency describes the qualitative

similarities and differences between the epidemiologic findings and the experimental toxicology database. In short, the observational studies – particularly those related to reproductive effects in adult females, as well as small for gestational age in newborns – lend further support for the human relevance of the laboratory animal findings.

a. Please comment on the scientific information that does and does not support the Agency's conclusions (as described in Section 3.0) with respect to the characterization of quality, and limitations of the non-cancer epidemiologic database and its utility in hazard characterization, dose response analysis, and quantitative risk assessment.

5:00 p.m. Charge to Panel

b. Please comment on scientific information that does and does not support the integrative analysis and conclusions, contained in Section 4.0, with respect to the similarities, differences, and uncertainties of the experimental toxicology and epidemiologic findings.

5:30 p.m. Meeting Adjourns

Day 3
Thursday, September 16, 2010

8:30 a.m. Opening of Meeting and Administrative Procedures – **Joseph Bailey**, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. Introduction and Identification of Panel Members – **Steven G. Heeringa, Ph.D.**, FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. Charge to Panel - Question 2.0 - Review of Studies on Mammary Gland Development

At the April SAP, the Agency evaluated effects of atrazine on a number of apical endpoints including neuroendocrine, neurotoxicity, and immunotoxicity effects. At that time, the Agency deferred review of experimental toxicology studies on mammary gland development to the September SAP meeting. Development of mammary tissue occurs in defined stages linked to sexual maturation and reproduction including embryonic, pre- and peripubertal periods, as well as pregnancy and lactation. Given that atrazine affects the hormonal environment and reproductive system, it is not unreasonable to hypothesize that it may also affect mammary gland development. The database of mammary gland development studies includes four studies---three from same the research group (Rayner *et al.*, 2004; Rayner *et al.*, 2005; Enoch *et al.*, 2007) in addition to one conducted by Coder (2010). It is important to note that the key events leading to reported delays in mammary gland development in the young following gestational exposure to atrazine are not known and none of these studies propose a mechanism/mode of action.

Question 2.1

The studies from the two different research groups yielded different results regarding the impact of atrazine on mammary gland development. While the Rayner and Enoch studies report delays in mammary gland development, the Coder study does not. The basis of these different findings is unknown. However, one notable difference in the study design used by the two research groups is the scoring system. The Rayner *et al*. and Enoch *et al.* studies used a subjective scoring scale with a 1-4 scoring system (1 = poor development/structure; 4 = normal development/structure) with criteria which vary depending on the age of the pups. In contrast, Coder employed a quantitative morphometric analysis to evaluate mammary gland development. In addition, the Coder study also included the use of BrDU labeling to assess cell proliferation in the mammary tissue.

Please comment on the quality, strengths, and limitations of the mammary gland development studies by Rayner et al. (2004, 2005) and Coder (2010) studies. Please discuss in your comments factors which could lead to different findings. Please comment on the Agency's conclusions regarding these studies on atrazine.

9:30 a.m. Charge to Panel

Question 2.2.

In three of the studies considered in Question 2.1 (Rayner et al., 2004 and 2005; Coder, 2010), effects have only been observed at an atrazine dose of 100 mg/kg/day. In contrast, Enoch *et al.* (2007) report delays in mammary gland development as low as 0.09 mg/kg/day following exposure to atrazine and a mixture of several metabolites/degradates (DEA, DIA, DACT, hydroxy-atrazine). The Agency's review of this mixture study is provided in Appendix A (Section A.10) Please comment on the Enoch *et al.* (2007) study and the degree to which the Agency's review accurately reflects the strengths and limitations of the study. Please include in your comments a consideration of the study design of the mixtures experiment and how this design impacts the interpretation of the results.

10:15 a.m. Break
10:30 a.m. Charge to Panel

Question 2.3.

As described in the Introduction of the draft Issue Paper (Section 1.0), the Agency's problem formulation is being conducted in a step-wise manner. One important component of this problem formulation is the evaluation of the overall database and the quality of the available experimental toxicology studies. In the case of mammary gland development, the Agency is proposing to acknowledge these four studies (Rayner *et al.*, 2004; Rayner *et al.*, 2005; Enoch *et al.*, 2007; Coder, 2010) in the hazard characterization but place little emphasis on them in its proposed updates to the dose-response assessment for atrazine. The only findings reported in the Rayner *et al.*, (2004), Rayner *et al.*, (2005), and Coder (2010) studies, occurred at a high dose (100 mg/kg/day) which is approximately 50-fold higher than the PoD of 1.86 for LH attenuation being proposed by the Agency. In the Enoch *et al.* (2007) study, there are significant limitations with the conduct and reporting the Agency believes which preclude the study from use in quantitative risk assessment.

In light of Panel discussion on Questions 2.1 and 2.2, please comment on the manner in which the Agency has proposed to use the mammary gland development studies in the hazard assessment for atrazine.

11:15 a.m. Charge to Panel - Question 3.0: Proposed Updates to the Dose-Response Assessment

At the April, 2010 SAP, the Panel made two key recommendations related to dose-response assessment: 1) consider pursuing a dose-response analysis based on an *internal* dose metric, as an alternative to the *administered* dose metric used in the previous risk assessment; and 2) identify the sensitive endpoint associated with functional impairment and perform benchmark dose (BMD) modeling. The Agency conducted both recommended analyses (Section 5.0 of the draft Issue Paper) in response to these recommendations. LH attenuation, as a key event in atrazine's MoA, is the most sensitive internal dose metric that is associated with a number of endocrinopathies

Question 3.1

Given that there is no robust pharmacokinetic model yet available, a non-compartmental analysis of the existing pharmacokinetic data was conducted and described in Section 5.2 of the draft Issue Paper. EPA thinks this represents the best method to estimate an internal dose metric without exceeding the limits of the available data.

a. Please comment on the Agency's analysis of the pharmacokinetic data contained in Thede (1987) to estimate internal dose reflective of atrazine and its metabolites in rat plasma.

11:45 a.m. Charge to Panel

b. Based on Figure 5.5 in the draft Issue Paper, the Agency has preliminarily concluded that plasma levels of atrazine and its metabolites reach (or nearly reach) pharmacokinetic pseudo-steady state in the rat plasma after approximately four daily oral exposures over a wide range of doses. Please comment on the extent to which the data do and do not support this finding.

12:15 p.m. Lunch
1:15 p.m. Charge to Panel

c. Figure 5.8 of the draft Issue Paper shows a plot of LH attenuation data versus administered atrazine across a range of exposure durations (i.e., four days up to six months). The data contained on this figure were collected from several different laboratories and involved two modes of oral administration (dietary, oral gavage) and two different rat strains. Attenuation of LH, as measured by percent of control, is remarkably similar across studies, strains, laboratories, and most notably duration of exposure. The Agency has preliminarily concluded that the findings on Figure 5.8 strongly support the hypothesis that *pseudo*-steady state is achieved (or nearly achieved) in adult rats after four daily consecutive oral exposures. The Agency also believes that *pseudo*-steady state is strongly associated with the attenuation of the LH surge following atrazine exposure in rats. Please comment on the analysis shown in Figure 5.8 and the Agency's preliminary conclusions related to these findings in rats.

2:00 p.m. Charge to Panel

Question 3.2

In Section 5.3, the Agency describes a benchmark (BMD) analysis conducted for LH attenuation studies. As described in the draft Issue Paper, the Agency initially considered a wide range of toxicological endpoints for inclusion in the BMD analysis. In considering all of the data, this analysis focused on studies measuring LH attenuation where female rats were exposed orally for four days and/or longer. This was not only the most sensitive endpoint but it's temporal and dose response are well defined experimentally. The LH effect originates from atrazine's effect on the hypothalamic control of pituitary function through its interference with GnRH neurotransmitters. Thus, protection from LH attenuation as a precursor event to several functional impairments would be protective of atrazine's neuroendocrine effects.

a. Please comment on the BMD analysis summarized in Section 5.3 of the draft Issue Paper with details provided in Appendix C.

2:45 p.m. Charge to Panel

b The selection of a suitable benchmark response (BMR) is an important component of conducting a BMD analysis. As described in Section 5.3, for continuous endpoints, like LH attenuation, the BMR most often represents an X% change from background levels (or untreated controls). Typically, the BMR is selected on the basis of a combination of biological (mode of action, quantitative link between key events and adverse outcomes, historical/concurrent controls) and statistical considerations (sample size, variability, etc). LH attenuation may be potentially associated with several adverse outcomes and the level of attenuation of the LH surge considered to be adverse is a function of several factors including the functional outcome and the life-stage. There is an absence of information concerning the level of response (or % change) associated with the various functional impairments. Also, the differences in reproductive cycles/aging between rodents and humans add an additional level of complexity to establishing a specific BMR value. When an X% change can not be defined, the Agency's draft BMD
guidance suggests that the BMD and BMDL corresponding to a change in the mean response equal to one standard deviation from the control mean be used as the BMR. This approach was applied to atrazine.

Please comment on the scientific factors important for establishing a BMR for LH attenuation as part of the BMD analysis for atrazine.

3:30 p.m. Break

3:45 p.m. Charge to Panel - Question 4.0: Approaches To Evaluating Water Sampling Strategies And Frequency Of Monitoring

The ultimate utility of pesticide monitoring data for drinking water exposure estimations in human health risk assessments depends on how well the monitoring data characterize the spatial and temporal variability of pesticide concentrations in drinking water, with an emphasis on the upper end of the exposure distribution. In addition, the method used to estimate concentrations from monitoring data depends on the duration of concern and how critical it is to estimate peak concentrations.

Question 4.1

A well-designed drinking water monitoring study takes into account both spatial and temporal patterns of exposure. Please comment on the USEPA's recommended framework for designing a monitoring study by targeting the most vulnerable areas, targeting seasonal times for more intensive sampling, basing sampling frequency on the toxicological exposure duration of concern, and using autosamplers to supplement monitoring data (see Section 7.2 of the draft Issue Paper).

4:15 p.m. Charge to Panel

Question 4.2

The April 2010 SAP recommended that simulations of candidate monitoring strategies and evaluations of the utility of different exposure estimation methods be benchmarked against intensive empirical data that cover a representative range of sites. In response, the USEPA proposes using more intensively sampled ambient water monitoring for flowing waters and PRZM/EXAMS modeling for static water bodies, matching them to the CWS based on similar chemograph shapes (see Section 7.3).

a. Please comment on the Agency's proposal to use chemograph shapes (number, duration, and magnitude of peaks) to match CWS with more intensively monitored datasets. In particular, the Agency is interested in recommendations on approaches for matching chemograph shapes given the loss of short-duration peaks that occurs with less frequent sampling.

4:45 p.m Charge to Panel

b. Please comment on the strengths and weaknesses of using more intensively sampled datasets from Heidelberg and AEEMP for analysis of flowing water and PRZM/EXAMS for lakes and reservoirs.

5:15 p.m. Meeting Adjourns

Day 4
Friday, September 17, 2010

8:30 A.M. Opening of Meeting and Administrative Procedures – **Joseph Bailey**, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 A.M. Introduction and Identification of Panel Members – **Steven G. Heeringa, Ph.D.**, FIFRA Scientific Advisory Panel Session Chair

8:45 A.M. Charge to Panel

Question 4.3

Once the magnitude and duration of exposure of toxicological concern are identified, the USEPA will determine which method(s) to use to analyze the existing atrazine CWS monitoring data for use in drinking water exposure estimates. Based on the April 2010 SAP recommendations, the Agency is focusing on regression-based modeling combined with random function modeling (for example, a revised WARP model coupled with kriging or the USGS SEAWAVE-Q model).

Please comment on the strengths and weaknesses of these proposed approaches and provide any recommendations for improving the model applications.

9:30 a.m. Charge to Panel

Question 5.0: Scientific Considerations in Potential Sensitivity of Infants & Children

As described in Section 6.0 in the draft Issue Paper, the FFDCA, as amended by the FQPA (1996), requires the Agency to give special attention to infants and children by placing emphasis on the availability of toxicology and exposure information to estimate the potential risk to these age groups. The 2003 Registration Eligibility Decision (RED) notes that the Agency reduced the FQPA Safety Factor for those localities which are part of the drinking water monitoring program conducted by Syngenta, as required by EPA. This reduction in the Safety Factor was based on more intensive monitoring required in the monitoring program that reduced the uncertainty for estimating concentrations of atrazine and its metabolites in drinking water for the 90-day rolling average identified in the previous risk assessment as the appropriate duration of concern. Based on the newest studies, our understanding of atrazine's temporal pharmacokinetic and pharmacodynamic characteristics has changed and it appears that shorter durations may be appropriate. In light of the potential need to shorten the critical duration of exposure and as discussed by the Panel in Questions 4.1-4.3, the Agency is evaluating appropriate methods for assessing the drinking water monitoring data.

Previously, the Agency noted data gaps related to "*information on Atrazine concerning exposure **throughout** all critical developmental periods (i.e., gestation through puberty in both sexes), in particular, early in development*…. (emphasis added, FQPA memo, 2002)." At the time of the previous risk assessment, there were only a few available studies which included measures sensitive to endocrine disruption on specific early life exposure periods (e.g., peripubertal). Since that time new studies have become available (Section 6.0) which add to the existing database and support the findings of the older studies. In addition, new tissue dosimetry studies provide information on the transfer of atrazine and its chlorinated metabolites to the fetus and to the lactating pup. Further, a study evaluating exposure to atrazine from multiple critical developmental periods identified previously by the Agency as a data gap is on-going. The results of this research will inform our understanding of the potential for differential life stage sensitivity.

In the coming months, as the drinking water exposure analysis develops further and the on-going toxicology studies become available, the Agency will work towards completing the scientific analysis that will inform whether or not a new FQPA Safety Factor should be applied in the atrazine risk assessment.

The Agency requests the Panel to comment on important scientific factors for the Agency to consider in its analysis. Please include in your comments specific consideration of uncertainties in estimating drinking water exposures and remaining uncertainties in atrazine's toxicological profile across life stages, particularly as they pertain to assessing risk to infants and children.

10:30 a.m. Break
10:45 a.m. Charge to Panel

Question 6.0: Implications of MOA & Toxicity Profile on Water Monitoring

As described in the Introduction of the draft issue Paper (Section 1), the goals of the current atrazine re-evaluation are: 1) to determine the extent to which new science indicates a need for the Agency to develop a revised human health risk assessment for atrazine and 2) to re-consider, as appropriate, the frequency of drinking water monitoring needed. Two important issues related to achieving these goals are determining the point of departure and identifying the critical effect and its associated duration of exposure. Proposed updates to the point of departure are considered in Questions 3.1 and 3.2. With respect to the critical duration of concern, the frequency of drinking water monitoring is related to the temporal pattern of the toxicological endpoint of concern used for the risk assessment. Generally, longer durations of toxicological concern (e.g., a long-term chronic effect) require a less frequent drinking water sampling design to approximate longer term exposures. However, as the duration of concern shortens, the frequency and timing of sampling become more important in determining how well the sample data capture short-duration exposures. Observation epidemiology studies raise hypotheses and suggest possible links between atrazine exposure and reproductive and developmental outcomes, but these epidemiology studies suffer from limitations which prevent firm conclusions. Although certain studies some provide qualitative support for the human relevance of the endpoints identified through the experimental toxicological database, they provide little to no information on the critical duration of exposure. In addition, the MOA and PK database are also lacking in human specific information on the effects of atrazine which could be used to quantitatively extrapolate between species. As such, the information available to evaluate the critical duration of exposure lacks quantitative precision. Thus, the critical duration of exposure is instead derived by inferring generic knowledge from a variety of scientific disciplines.

The Agency has used a variety of approaches to extrapolate findings from experimental animal data to humans including allometric scaling and human-specific information on the physiology of the menstrual cycle inferred from the IVF literature. According to the Agency's analysis of the pharmaceutical data and allometric scaling of the rodent pharmacokinetics data, the potential durations of human exposure that would correspond to the exposure period of interest in rats lie between a few days to approximately 4 weeks of exposure.

Please comment on the Agency's analysis and preliminary conclusions contained in Section 8.0 of the draft Issue Paper as it relates to the potential critical windows of exposure. Please include in your comments additional or alternative approaches or data that may inform this issue.

12:00 p.m Lunch
1:00 p.m. Charge to Panel continued
3:00 p.m. Break
3:15 p.m. Charge to Panel continued
5:00 p.m. Adjourn

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Joseph Bailey, via telephone: (202) 564-2045; fax: (202) 564-8382; or email: bailey.joseph@epa.gov